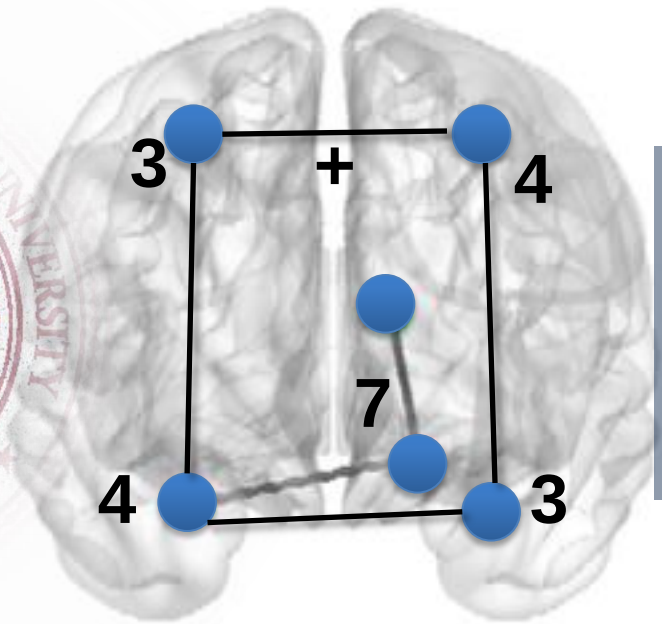
Training the "Mathematical Brain": evidence from functional brain imaging and neuro-modulation techniques



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Stanford University School of Medicine
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Overview

Neuro-imaging techniques

functional Magnetic Resonance Imaging (fMRI)

Multivariate approaches

Neuro-modulation techniques

transcranial Direct Current Stimulation (tDCS)

Neuro-rehabilitation

Brain Plasticity Learning

Biomarkers **Brain Organization**

Individual Differences

Developmental Dyscalculia

UNIVERSITY OF OXFORD

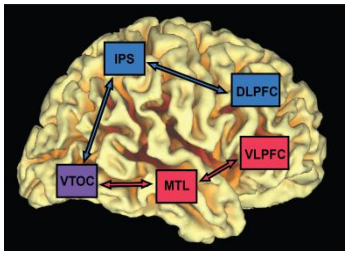
Developmental Dyscalculia

- **Neurodevelopmental learning disability**
- **3 to 7% of individuals**
- **Difficulties in dealing with numbers and performing arithmetic**
- **Significant effects on educational and social outcomes**
- **Crucial to intervene to alleviate poor performance in these learners**

Introduction

- Classroom-based and individual-based **behavioral training** could be **effective**, yet the **neurobiological mechanisms** underlying successful intervention are **unknown** *(Dowker et al., 2004; Fuchs et al., 2008, 2009, 2013)*

- **Math learning** is supported by a **host** of **brain systems** including those serving numerical, mnemonic, visuo-spatial and executive functions



(Menon, 2014)

- **Developmental Dyscalculia (DD)** has been characterized as a condition reflecting **structural** and **functional brain abnormalities** *(Butterworth, 2011, Fias et al., 2014)*

- Uncovering **brain plasticity effects** by **tracking** the **functional brain changes** following effective intervention **could inform on**:

(i) which **aspects** of **cognition** are i**mpaired** in **DD** during math problem solving,

(ii) which of these **mechanisms** could be **strengthened** as a result of intervention

Research Questions

1. Can **8 weeks** of math **tutoring remediate behavioral performance** in **DD**?

2. Can **8 weeks** of math **tutoring** elicit **neuroplasticity effects** in **DD?**

3. If **neuroplasticity** effects occur, **would their signature be characterized by**:
   (i) *neural normalization*, or *(ii)* *neural compensation*?

4. Is there a **systematic relation** between **tutoring-induced neuroplasticity** and **behavioral improvement**, if any, in **DD**?

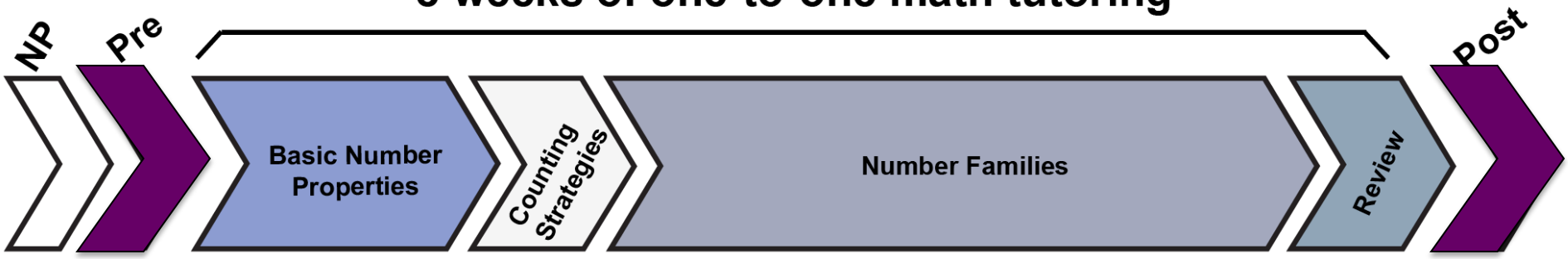
Methods and Material

Multi-criteria diagnosis of DD: (i) *Normed-based cut-off criterion*; (ii) *Discrepancy criterion*

Measure	**DD (N = 15)**	**TD (N = 15)**	**p - value**
Male to Female ratio	6 : 9	7 : 8	
Age (years)	8.65 (0.47)	8.54 (0.49)	0.52
IQ – WASI scale			
Full IQ	*100.33 (10.67) ****	107.47 (11.05)	0.08
Verbal IQ	103.40 (13.80)	106.60 (15.68)	0.56
Performance IQ	97.53 (15.08)	106.73 (11.18)	0.07
WIAT – II			
Numerical Operations	*80.93 (4.25) ****	105.80 (9.53)	*0.00001 ****
Math Reasoning	*90.80 (9.19) ****	106.20 (9.36)	*0.0001 ***
Word Reading	100.20 (9.67)	106.27 (9.01)	0.09
Reading Comprehension	102.27 (7.87)	108.07 (11.11)	0.11
WMTB – C			
Digit Recall	97.71 (10.82)	99.13 (17.75)	0.79
Block Recall	88.00 (18.39)	93.20 (17.59)	0.31
Count Recall	77.61 (15.07)	86.71 (14.61)	0.15
Backwards Digit Recall	87.93 (9.55)	92.93 (15.21)	0.23

Methods and Material

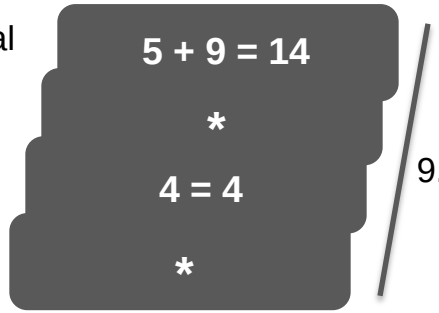
8 weeks of one-to-one math tutoring



fMRI

Math problem solving

Addition trial
Fixation
Control trial
Fixation
…



9.5 secs

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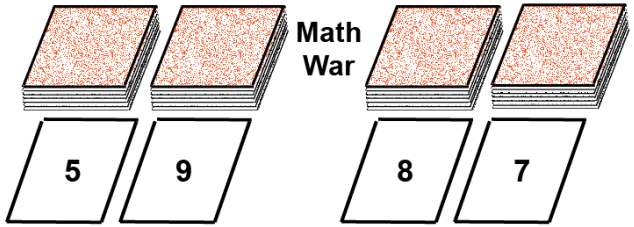
MATH GAMES

Math Bingo

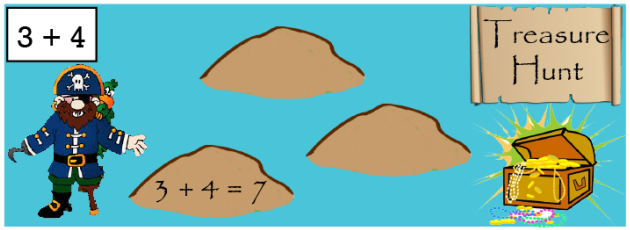
"Find the answer on the Bingo card"

5 + 5

Facilitate arithmetic fluency and strengthening number knowledge *(Fuchs et al., 2008, 2009, 2013)*

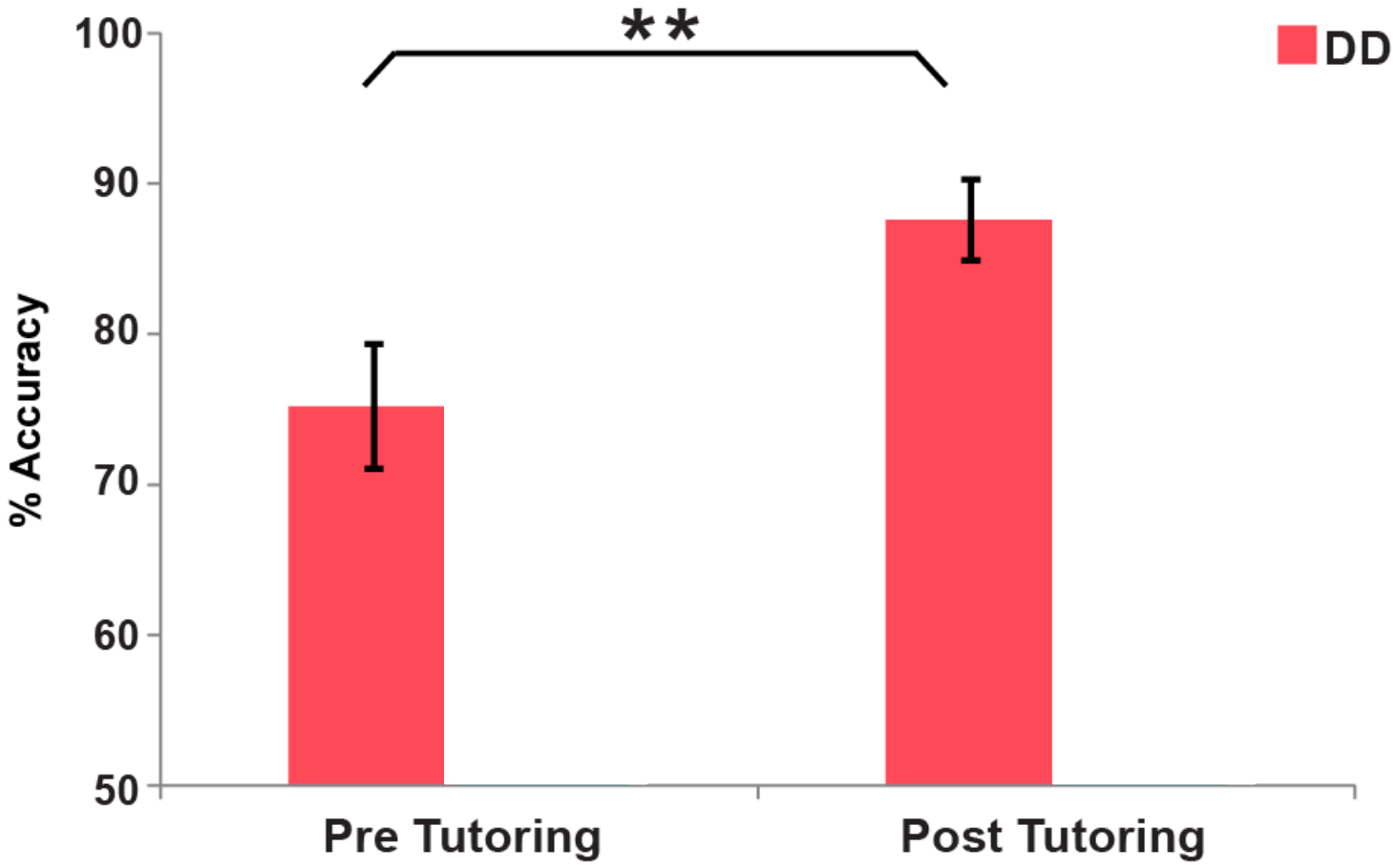


3 times per week
40-50 min



Iuculano et al., under review; Supekar et al., 2013

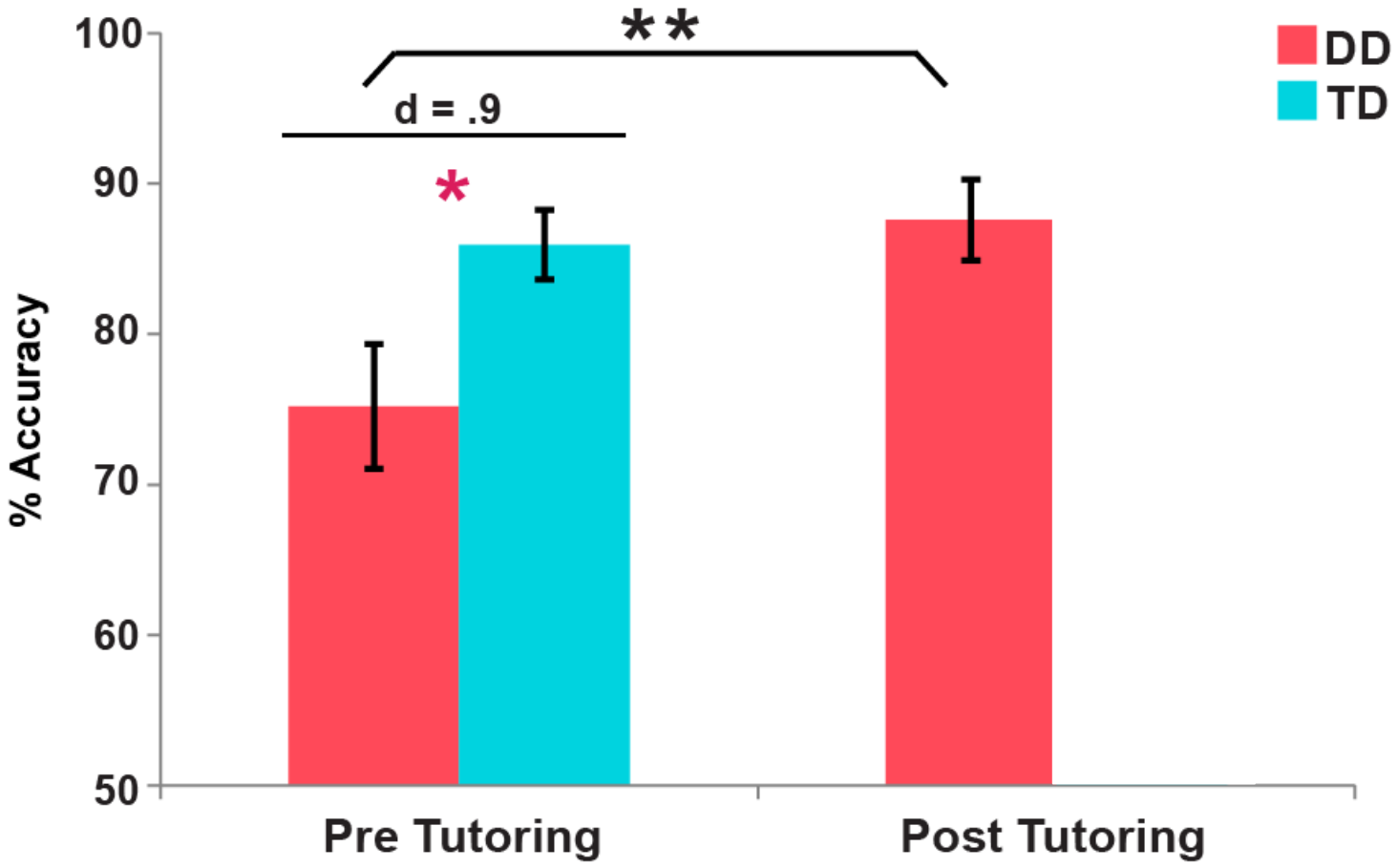
Results – Behavioral performance



Following 8 weeks of 1:1 **tutoring** children with **DD** showed **significant** **<u>performance improvement</u>** in math problem solving

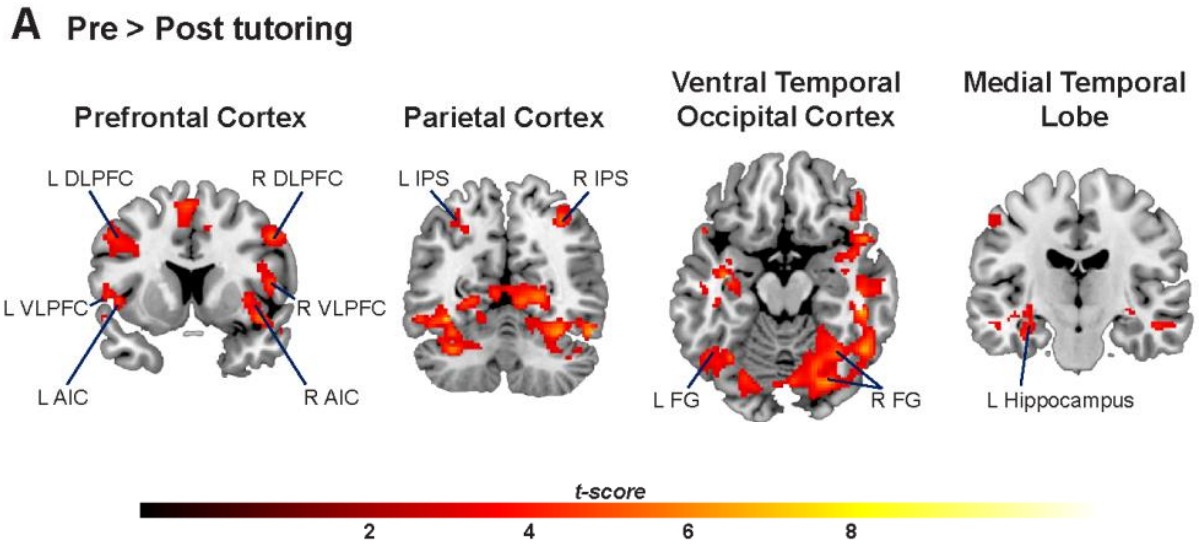
Iuculano et al., under review

Results – Behavioral performance

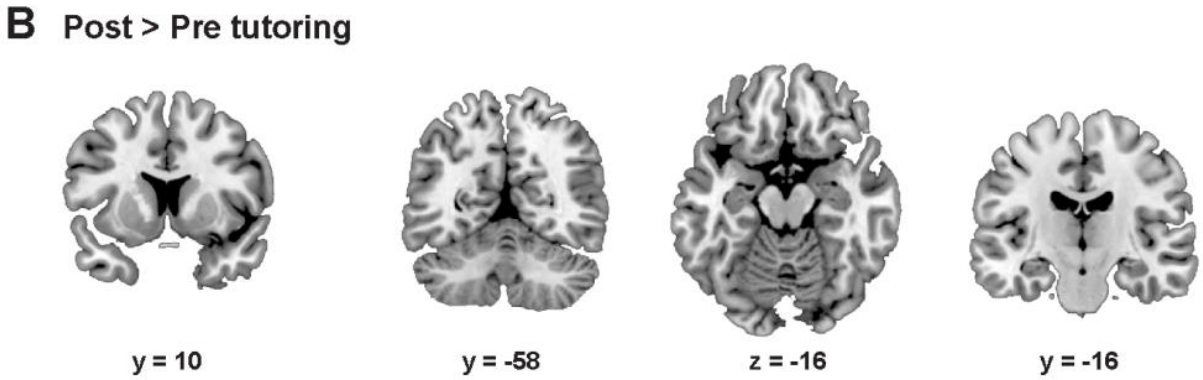


Performance normalization in DD. Group-differences in performance before tutoring were no longer evident after tutoring

Results – Functional neuroplasticity

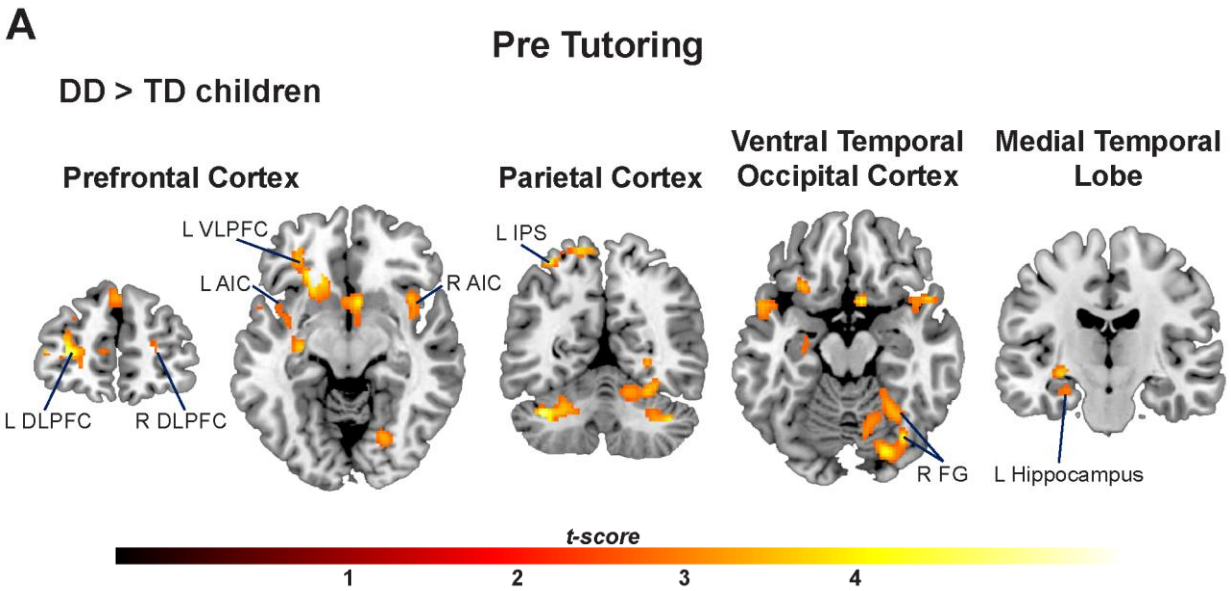


Before tutoring children with **DD** showed **over-activation** in multiple brain areas of the Prefrontal Cortex (**PFC**), Posterior Parietal Cortex (**PPC**), Ventral Temporal-Occipital Cortex (**VTOC**) and Medial Temporal Lobe **(MTL**)

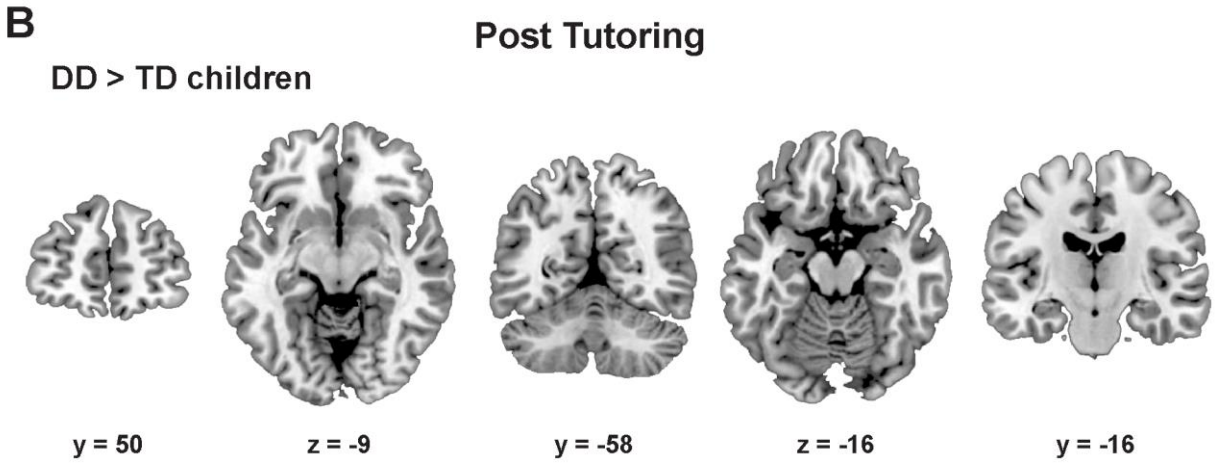


No brain areas showed **higher activation after tutoring** in **DD**

Results – Functional normalization



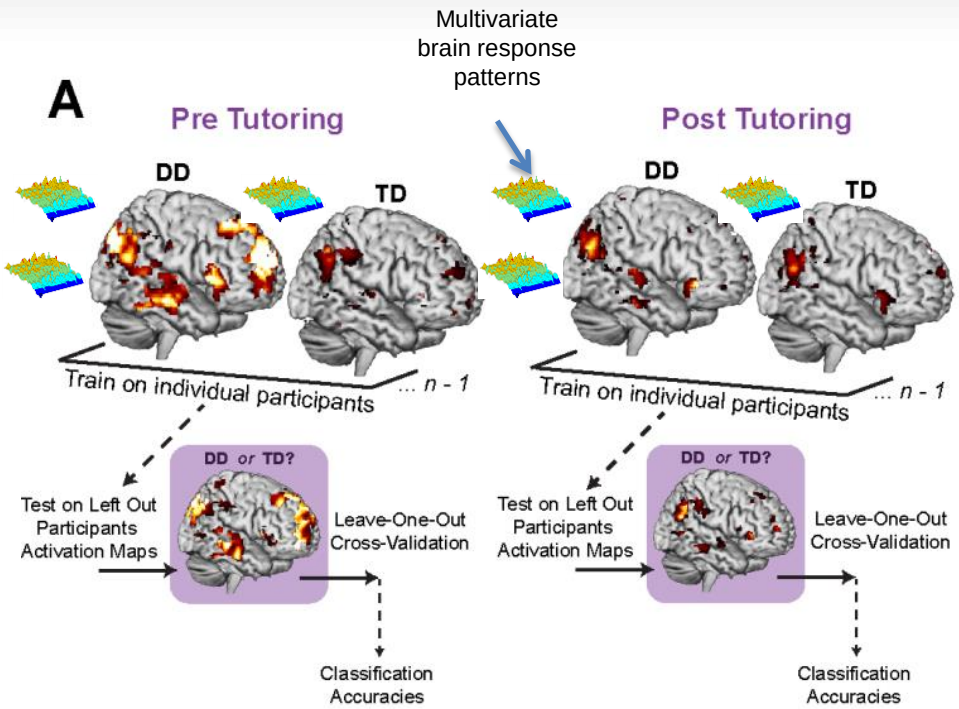
Before tutoring children with **DD** showed **over-activation** in multiple brain areas of the **PFC**, **PPC**, **VTOC** and **MTL**, compared **to TD children**



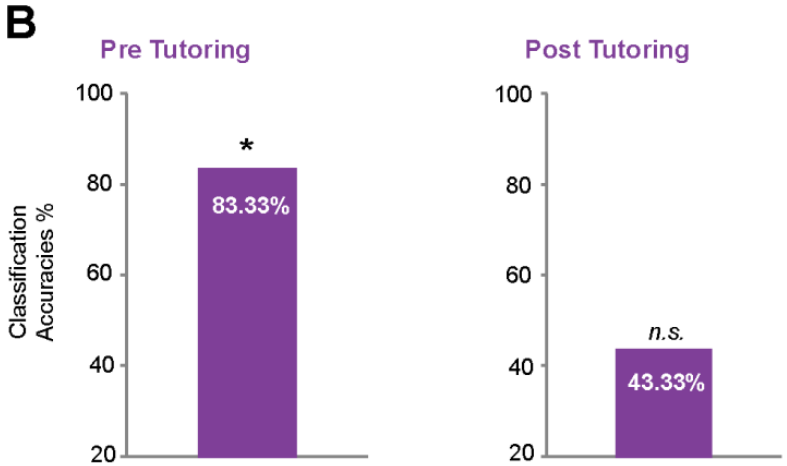
After tutoring no differences were evident between **DD** children and their **TD** control peers

Iuculano et al., under review

Results – Multivariate Pattern Analyses – Quantifying functional normalization



We asked whether functional activity patterns during arithmetic problem solving could be use to **discriminate** the **brains** of **DD** children **from** those of **TD** children **before** and **after tutoring**

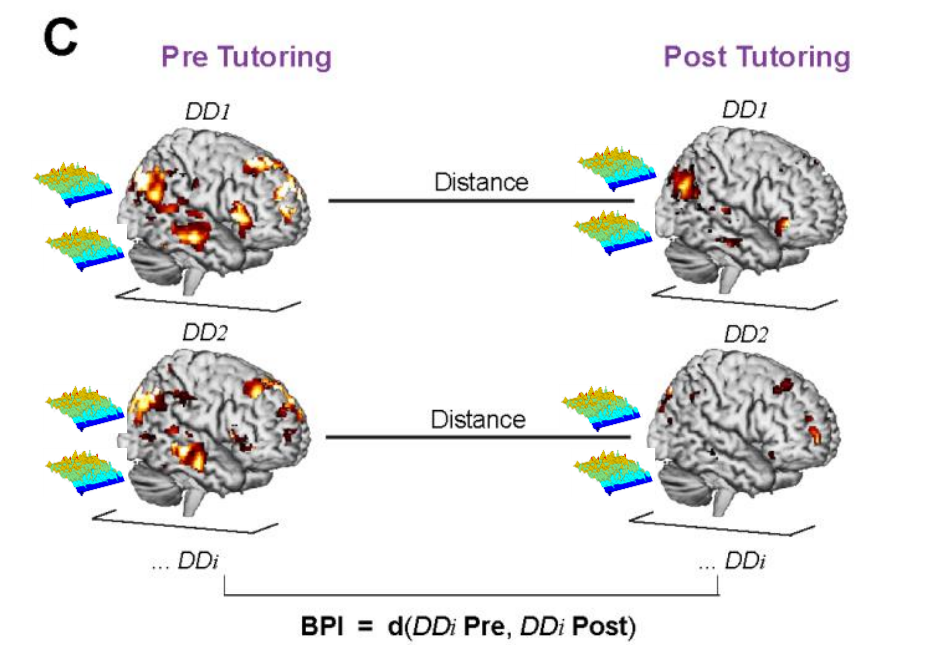


Functional **activity patterns** during arithmetic problem solving were sufficient and significantly able to **accurately discriminate** children with **DD from TD** children **before tutoring**, **but not after tutoring,** where the algorithm performed worse than chance.

Iuculano et al., under review

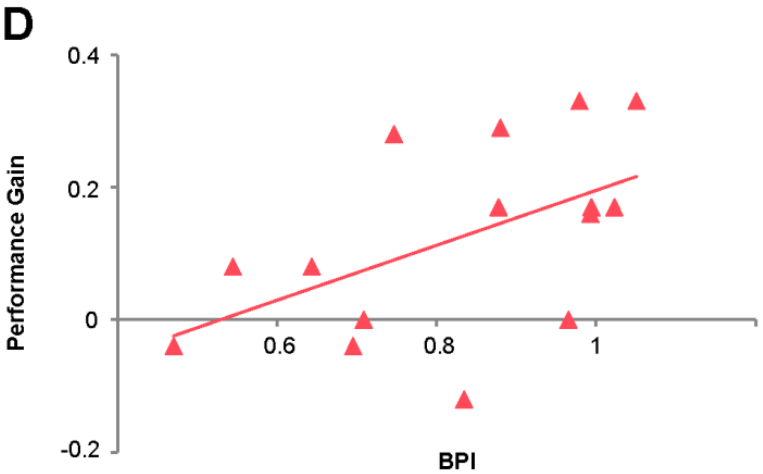
Results – Neurobehavioral correlates of tutoring outcomes

Brain Plasticity Index (BPI) = Multivariate spatial correlation between pre- and post- tutoring activity patterns in DD



Does **BPI** relate to **better performance gains** in **DD?**

Yes, the more the brain changes, the better the performance in DD



None of the **domain-general** standardized **measures** (IQ, WM)**,** nor **math standardized measures** significantly **predicted** performance **improvement in DD.**

Iuculano et al., under review

Interim - Summary

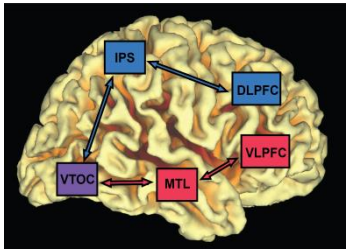
1. Can **8 weeks** of math **tutoring remediate behavioral performance** in **DD**?

Yes, *consistent with previous classroom-based studies*, math tutoring focused on conceptual knowledge and speeded practice ***can remediate poor math performance*** *in* children with ***DD***

2. Can **8 weeks** of math **tutoring** elicit **neuroplasticity effects** in **DD?**

Yes, 8 weeks of ***effective behavioral tutoring can elicit*** neuroplasticity effects in children with ***DD***

Tutoring-related effects were evident ***in multiple brain systems*** *supporting the hierarchical cascade of cognitive computations necessary for successful math problem solving*



3. If **neuroplasticity** effects occur, **would their signature be characterized by**: *(i)* <u>*neural normalization*</u>, or *(ii)* <u>*neural compensation*</u>?

Neuroplasticity effects support the ***neural normalization*** hypothesis***: prominent differences between the groups were evident*** - in an univariate as well as multivariate sense – ***before but not after tutoring***

4. Is there a **systematic relation** between **tutoring-induced neuroplasticity** and **behavioral improvement**, if any, in **DD**?

Yes, the degree of neuroplasticity was significantly ***related*** to ***individual differences*** *in* ***performance gain*** after tutoring ***in DD***

Introduction

- **DD often persists into adulthood**
- **Learners** diagnosed with **DD at** age **11, over 40%** were **still** in the **DD** category **at** age **17** *(Shalev et al., 2005)*
- **High IQ, verbal and memory** abilities could **help** these individual **progress through education**, yet the **social outcome** of **adult DD** is as **severe** and equally **alarming** as it often **manifests** in **every day** life situations

Check bills

Pick the right type of mortgage

Decide if something is too heavy

Remember PIN numbers

Talk about prices

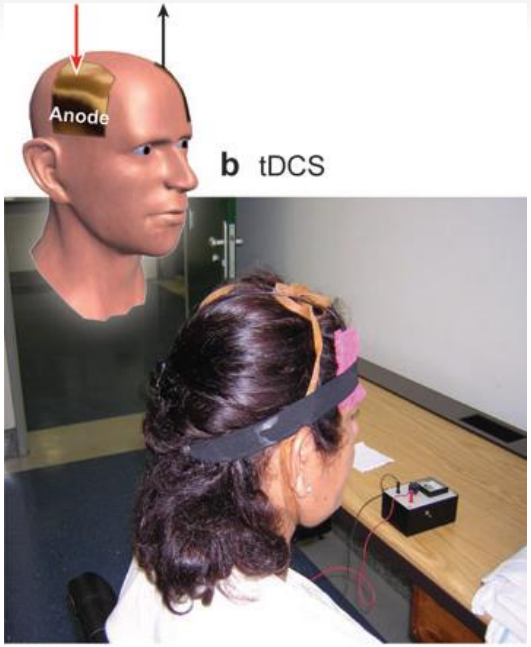
Catch the right bus

Gerardi et al., 2013, PNAS

Introduction

Math-based intervention during the **early** school **years** is **effective**, but in **adults** with **DD** such type of intervention is *(i)* **unfeasible;** *(ii)* likely **ineffective** as **brain circuits** might have **re-organized differently after** many **years** of “bad math”

tDCS



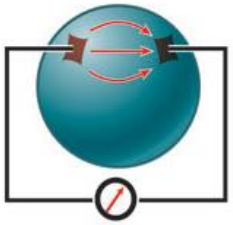
Neuro-modulation technique

Low-amplitude direct currents – applied via scalp electrodes – act on **polarization-dependent mechanisms** of resting membrane potential.

Anodal stimulation **increases excitability by pushing** neural resting membrane potentials closer **to the activation threshold**

Cathodal stimulation – the reverse polarity – **inhibits** cell firing **and decreases excitability**

DC current applied via pair of electrodes; current induced in conductor



Wagner et al. 2007

tDCS

THE JOURNAL OF
CLINICAL PSYCHIATRY

Transcranial Direct Current Stimulation for Refractory Auditory Hallucinations in Schizophrenia

Chittaranjan Andrade, MD

Exp Brain Res (2013) 226:25–31
DOI 10.1007/s00221-013-3406-7

RESEARCH ARTICLE

Comparing immediate transient tinnitus suppression using tACS and tDCS: a placebo-controlled study

Sven Vanneste · Vincent Walsh · Paul Van De Heyning · Dirk De Ridder

Current Biology *20*, 1–5, November 23, 2010

Report

Modulating Neuronal Activity Produces Specific and Long-Lasting Changes in Numerical Competence

Exp Brain Res (2005) 166: 23–30
DOI 10.1007/s00221-005-2334-6

RESEARCH ARTICLE

Felipe Fregni · Paulo S. Boggio · Michael Nitsche
Felix Bermpohl · Andrea Antal · Eva Feredoes
Marco A. Marcolin · Sergio P. Rigonatti
Maria T.A. Silva · Walter Paulus
Alvaro Pascual-Leone

Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory

ranscranial Direct Current Stimulation (tDCS) Decreases ıdes of Long-Latency Stretch Reflexes in Cerebellar Ataxia

Giuliana Grimaldi and Mario Manto
Mouvement (UEM), ULB-Erasme, ULB Neurologie 808 Route de Lennik, 1070 Bruxelles, Belgium

(Received 9 April 2013; accepted 12 June 2013; published online 19 June 2013)

Associate Editor Xiaoxiang Zheng oversaw the review of this article.

Transcranial Direct Current Stimulation for Major Depression: A General System for Quantifying Transcranial Electrotherapy Dosage

Marom Bikson, PhD
Peter Bulow, MD, MFA

Kang and Paik *Experimental & Translational Stroke Medicine* 2011, **3**:4
http://www.etsmjournal.com/content/3/1/4

EXPERIMENTAL & TRANSLATIONAL STROKE MEDICINE

RESEARCH Open Access

Effect of a tDCS electrode montage on implicit motor sequence learning in healthy subject

Eun Kyoung Kang[1] and Nam-Jong Paik[1,2*]

Efficacy of semantic–phonological treatment combined with tDCS for verb retrieval in a patient with aphasia

Rosa Manenti[a], Michela Petesi[a], Michela Brambilla[a,b], Sandra Rosini[a], Antonio Miozzo[c], Alessandro Padovani[c,d], Carlo Miniussi[a,d] and Maria Cotelli[a*]

Research Question

Could numerical abilities in persistent DD be effectively modulated by the application of neuro-modulation techniques – such as tDCS – applied together **with a learning paradigm?**

Methods and Material

Measure	Individual DD	
	DD1	***DD2***
Age (years)	33	26
DOMAIN-GENERAL ASSESSMENTS		
IQ – WAIS scale		
Full IQ	92	118
Verbal IQ	91	114
Performance IQ	96	121
Visuo-spatial skills-WAIS		
Block design[a]	13	15
DOMAIN-SPECIFIC ASSESSMENTS		
Dyscalculia screene[b]		
Simple RTs	**1**	4
Capacity subscale	3.5	**2.5**
Dot enumeration	**1**	4
Number comparison	8	**1**
Achievement subscale	**1**	3.5
Addition	**1**	4
Multiplication	**1**	**3**
GDA[c]	8 [**3**]	9 [**3**]
Non-symbolic number comparison		
WF[d]	**0.64**	**0.26**
Arithmetical test - WAIS		
Arithmetic	**50%ile**	**50%ile**

Methods and Material

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Age (years)	33	26
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Addition	**1**	4
Multiplication	**1**	**3**
GDA[c]	8 [**3**]	9 [**3**]
Non-symbolic number comparison		
WF[d]	**0.64**	**0.26**
Arithmetical test - WAIS		
Arithmetic	**50%ile**	**50%ile**

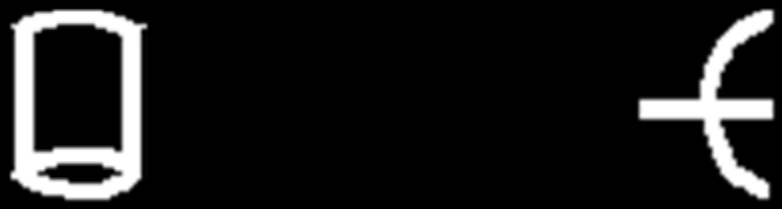
Artificial digits

1	2	3	4	5	6	7	8	9
								

Iuculano & Cohen Kadosh, 2013

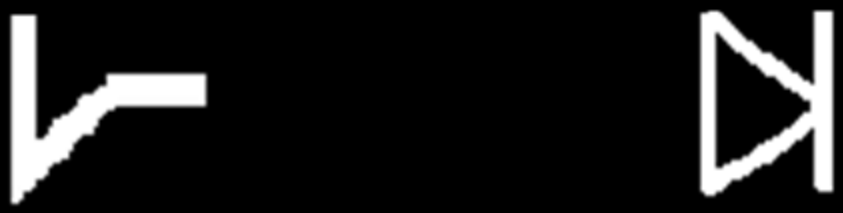
Learning task

*



Correct

*



Mistake

Methods and Material

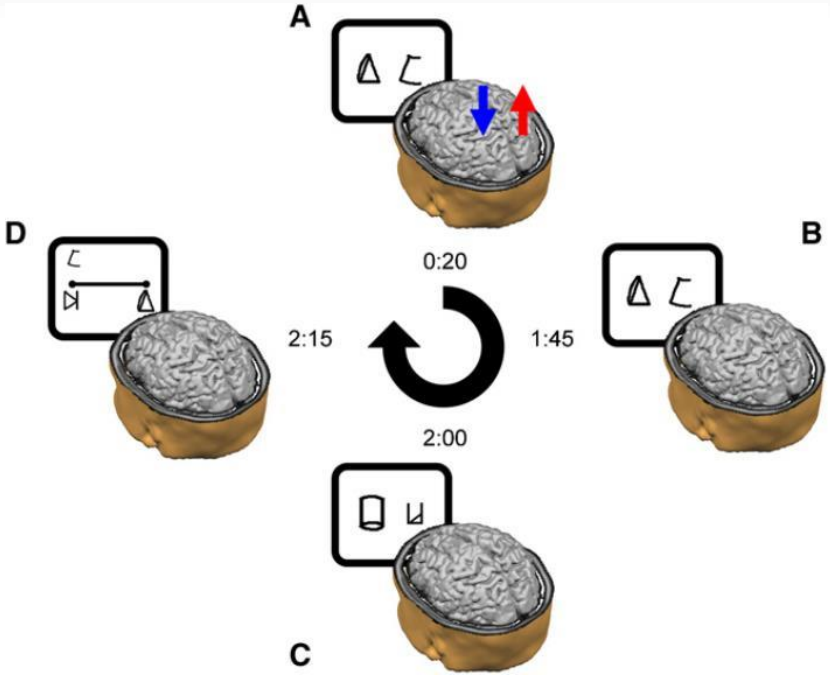
I. tDCS was delivered for **20 min** from the start of the training

The **training continued after** the termination of **the stimulation**

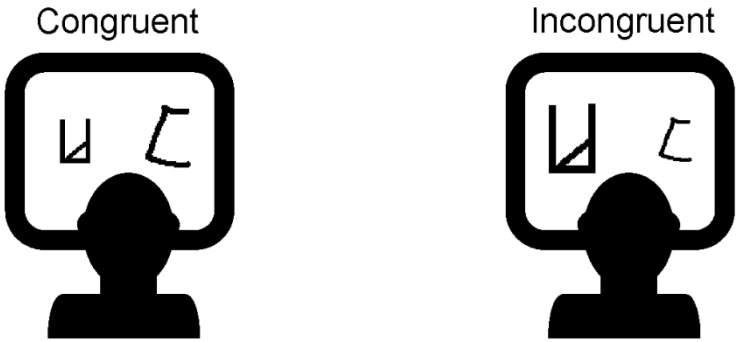
II. Once the training ended, the subject performed a **Numerical Stroop task**

III. and a **Number Line task**

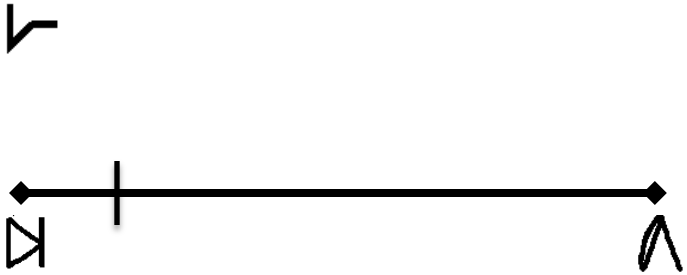
I.



II.

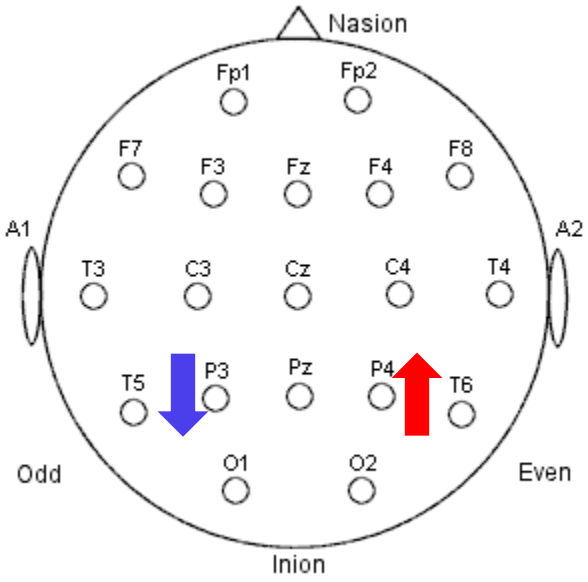


III.



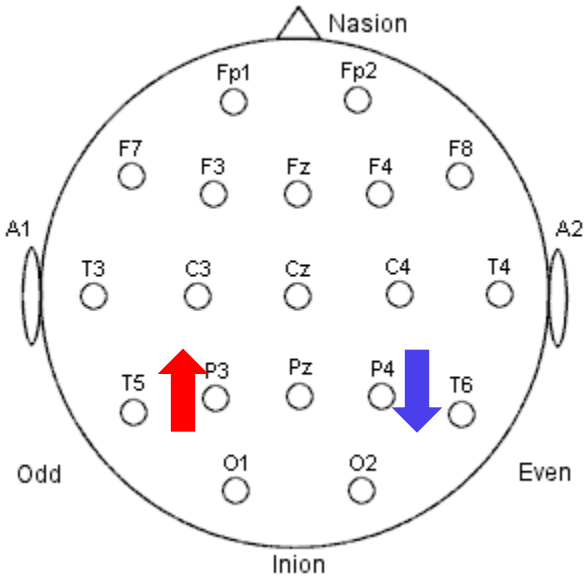
tDCS - Montage

DD1



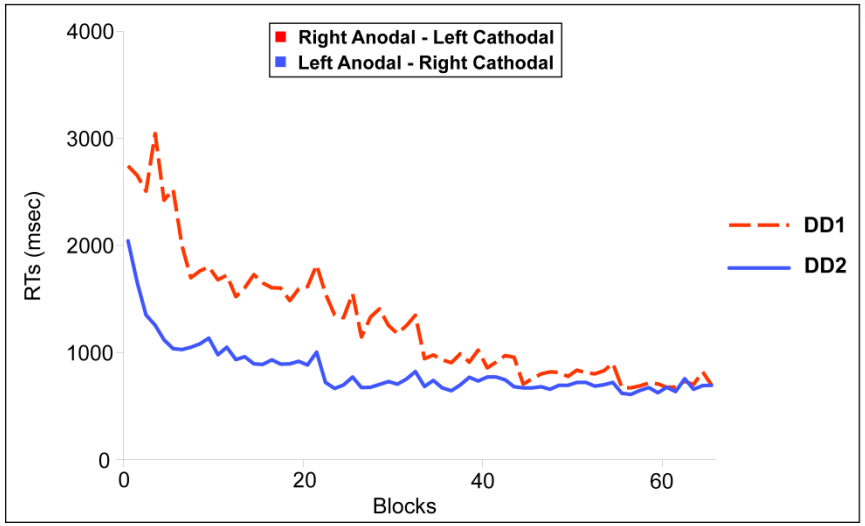
RA-LC

DD2

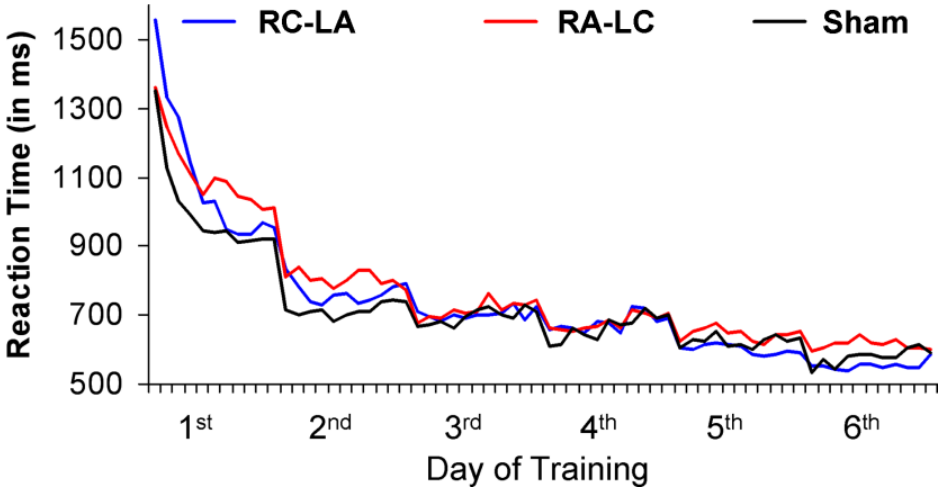


LA-RC

Results – Learning curves

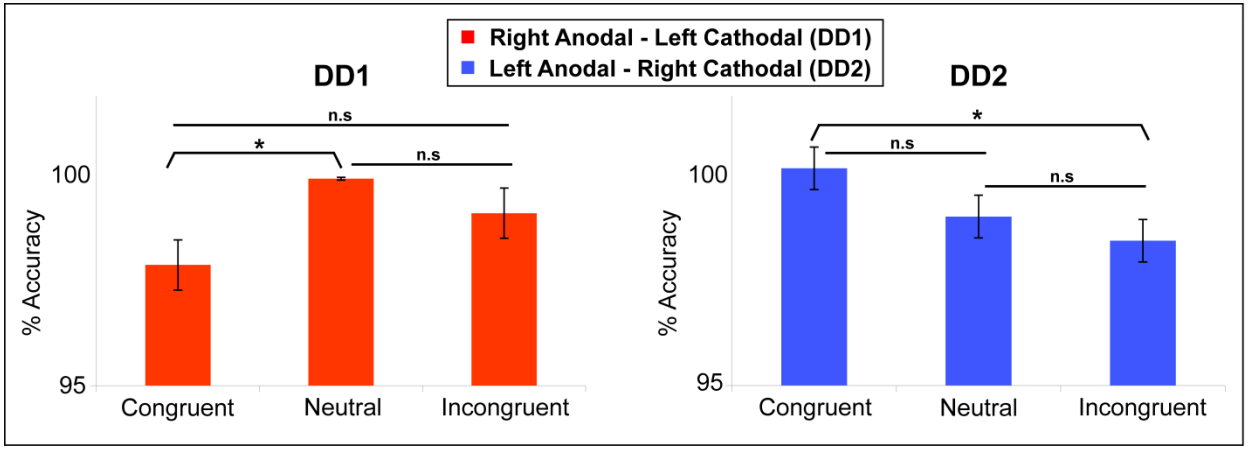


Equivalent fit for both DD1 and DD2

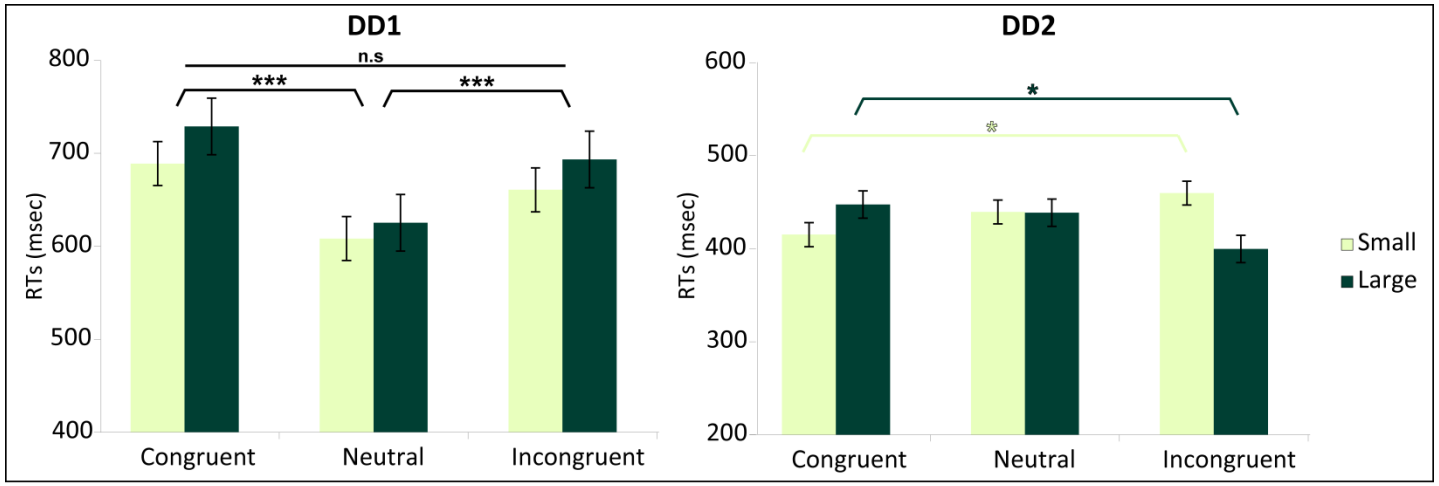


Performance of both DDs was also **equivalent** to **healthy controls**

Results – Numerical Stroop task

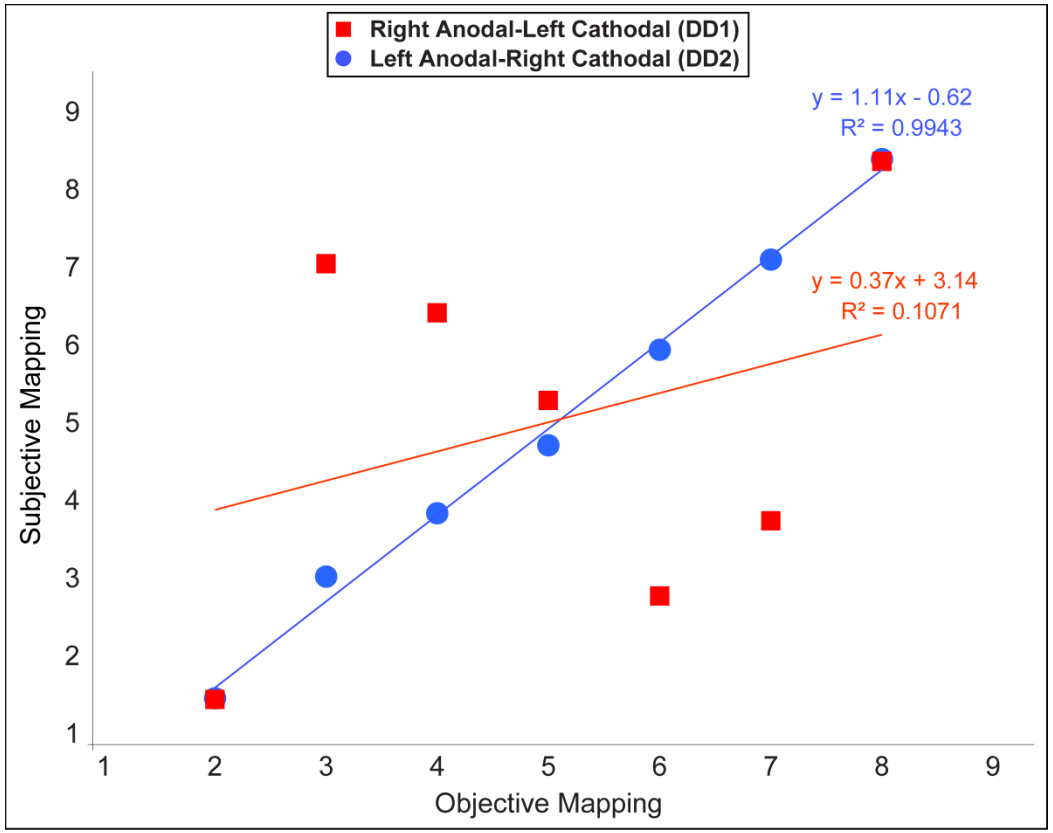


DD2 exhibited the canonical **Congruecy effect** (Congruent > Neutral > Incongruent)
DD1's performance was **not** modulated by numerical information (Neutral > Congruent)



DD2 showed a **Congruency effect** related to the **numerical distance** between stimuli;
<u>while for</u> **DD1** the Neutral condition was always the easiest

Results – Number Line task



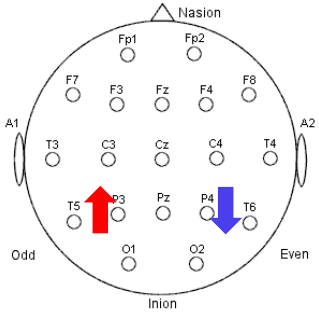
- **DD2** showed a **linear fit** in mapping the artificial digits
- **DD1** did **not**

Interim - Summary

Could numerical abilities in persistent DD be effectively modulated by the application of neuro-modulation techniques – such as tDCS – applied together **with a learning paradigm?**

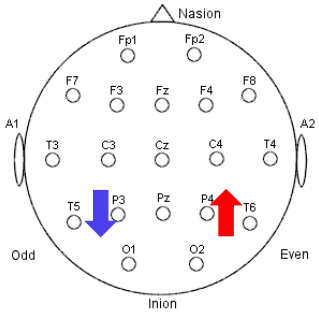
Yes, neuromodulation techniques accompanied by learning paradigms could be effective in remediating performance in adults with DD

Successful tDCS montage for DD



Iuculano & Cohen Kadosh, 2013

Successful tDCS montage for healthy adults



Cohen Kadosh et al., 2010

This could reflect: (i) variability between DD cases both in terms of performance as well as brain morphology – need for ***ad–hoc* stimulation *(?)***

(ii) neural-reorganization/plasticity effects reflected by **inter-hemispheric compensation** ➡ tDCS might up-regulate the excitability of the compensatory mechanisms while down-regulating the impaired contro-lateral area

Conclusions

- **Brain-based measures** can provide a sensitive **biomarker** for diagnosis as well as response to treatment for DD

- **The unique contribution** of **neuroscience-based approaches** to guide intervention practice in DD, pointing to specific **brain systems** that can be fruitfully **targeted** for improving skills of **weak-responders**

Stanford Cognitive and Systems Neuroscience Laboratory

The kids

and their families

Dr. Roi Cohen Kadosh

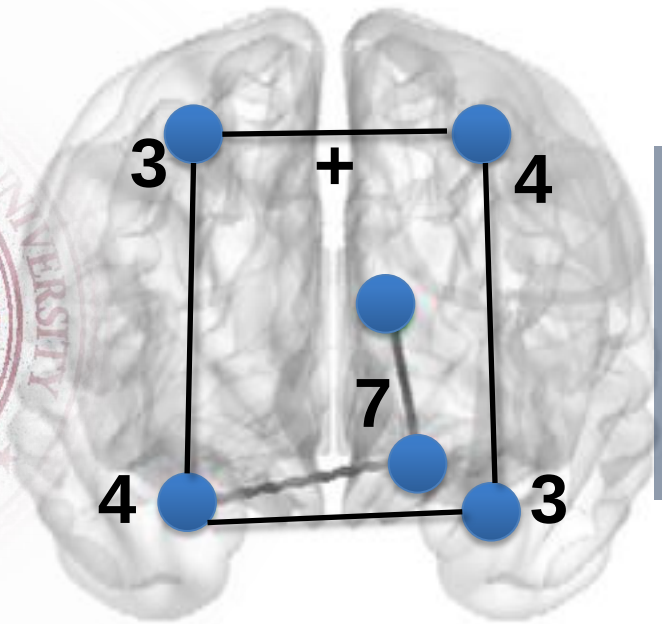
UNIVERSITY OF OXFORD

Funding Sources

- ***National Institutes of Health***
- ***Stanford Institute for Neuroscience***
- ***Singer Foundation***

Thank you

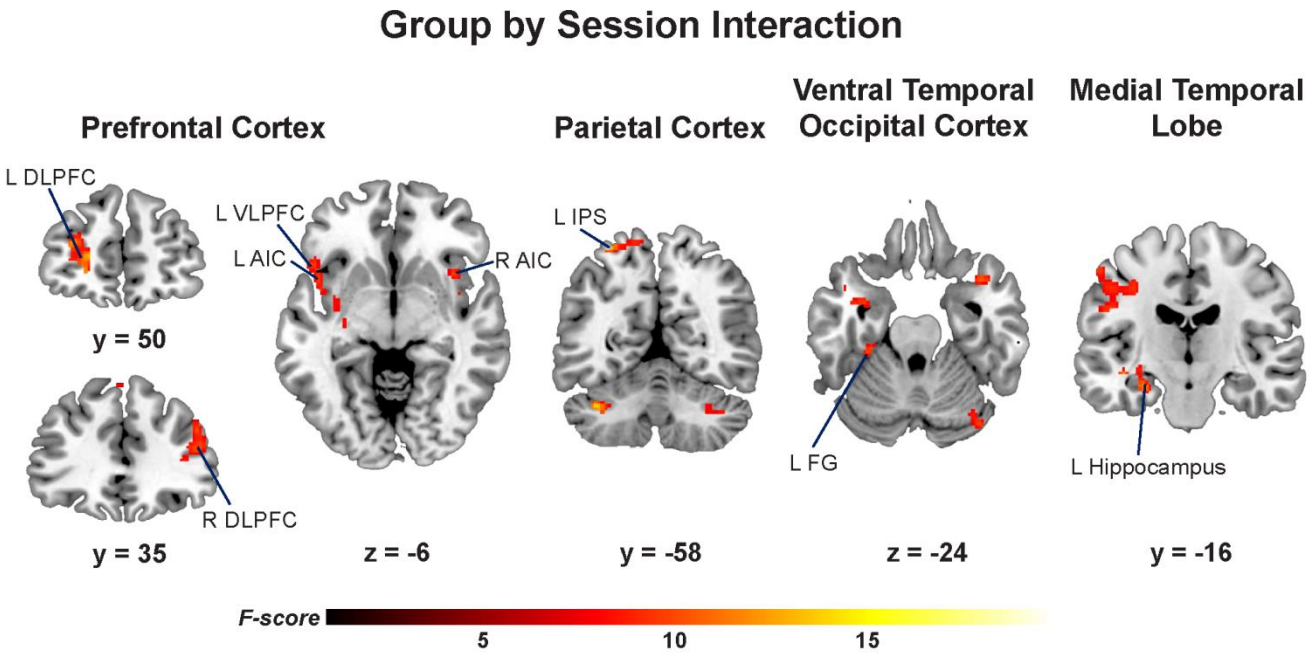
Training the "Mathematical Brain": evidence from functional brain imaging and neuro-modulation techniques



Teresa Iuculano, Ph.D.
Stanford Cognitive and Systems Neuroscience Laboratory
Stanford University School of Medicine
Email: ***teresai1@stanford.edu***

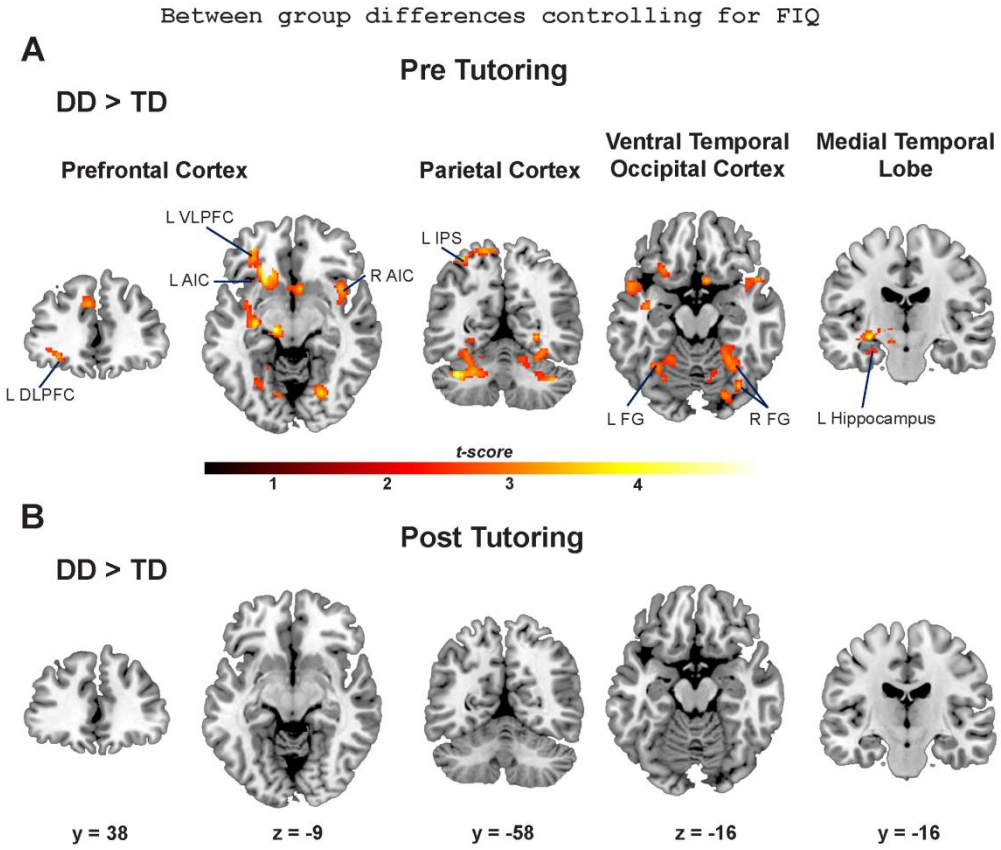
Extra Slides

Results – ANOVA model



Iuculano et al., under review

Results – Control analyses – *FIQ scores*



Iuculano et al., under review

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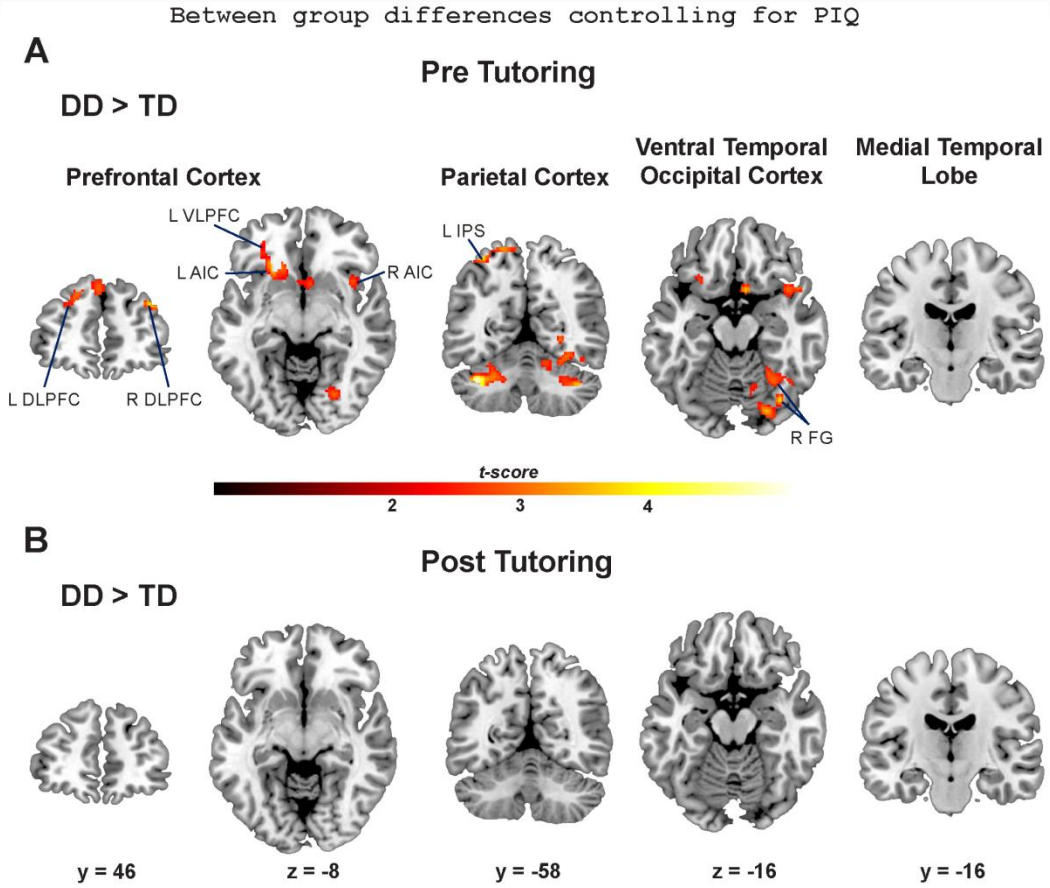
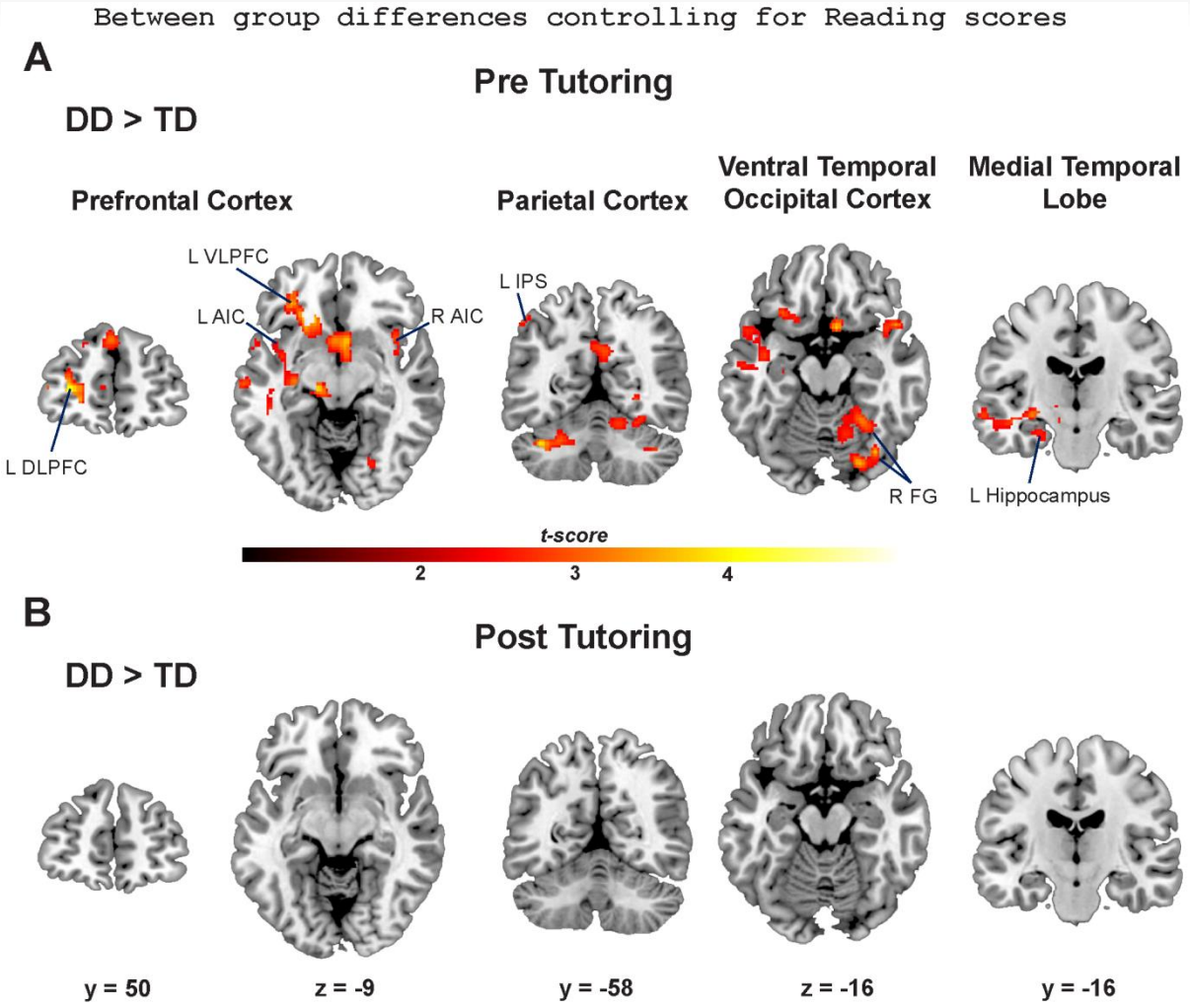


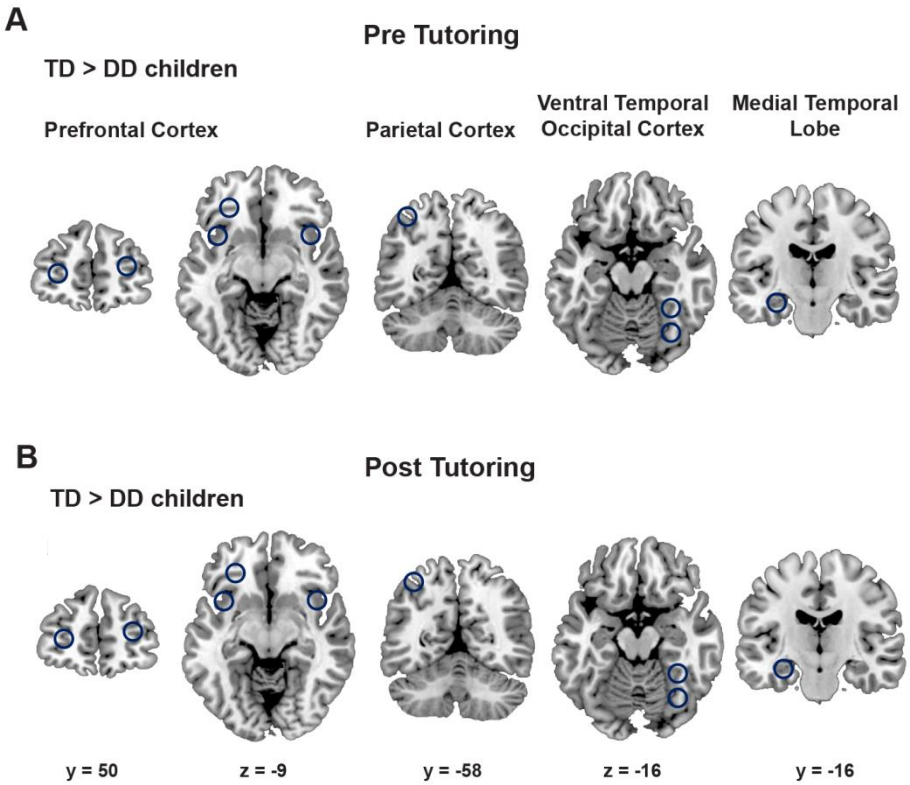
Iuculano et al., under review

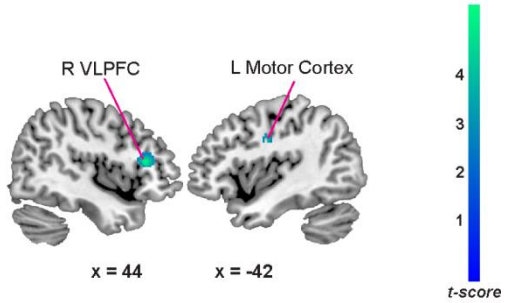
Results – Control analyses – *Reading scores*



Iuculano et al., under review

Results – Post-tutoring differences – *TD > DD*





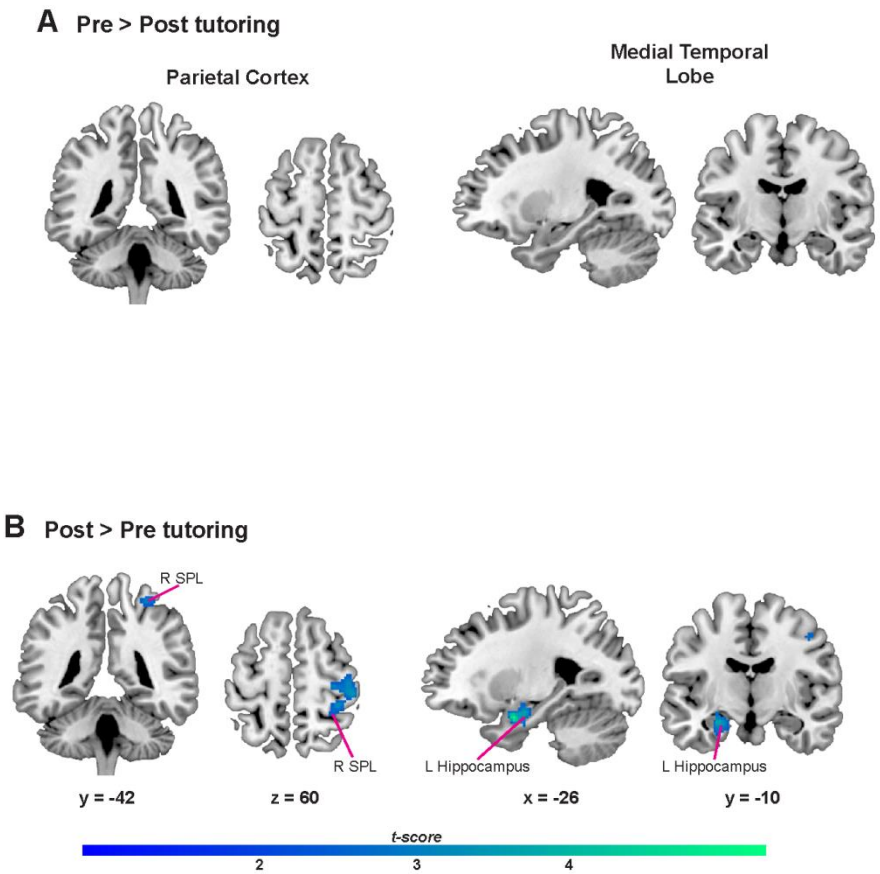
Before tutoring children with **DD** showed **over-activation** in multiple brain areas of the PFC, PPC, VTOC and MTL, compared to TD children

After tutoring **no differences** were evident between DD children and their TD control peers

Iuculano et al., under review

Results – TD children – *Post* > *Pre*

Figure S2 *– Within group analyses.* ***(C)*** *TD: No brain areas showed higher activation levels before, compared to after, tutoring;* ***(D)*** *After 8-weeks tutoring TD showed increased activation levels in areas of the parietal cortex and MTL.*



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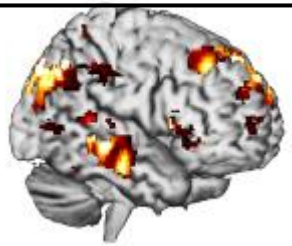
Iuculano et al., under review

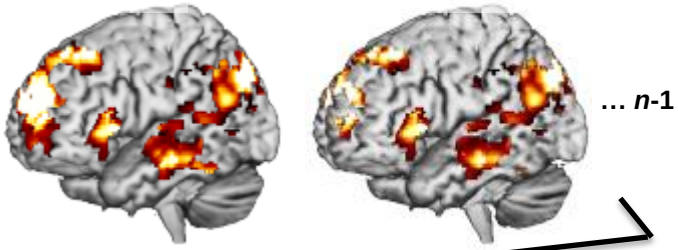
MVPA analyses

fMRI during math problem solving

Brain activation maps

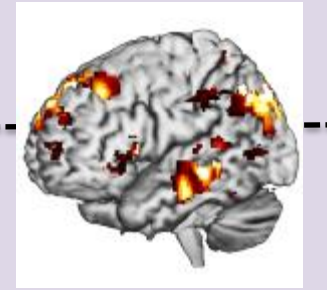


Multivariate pattern analysis



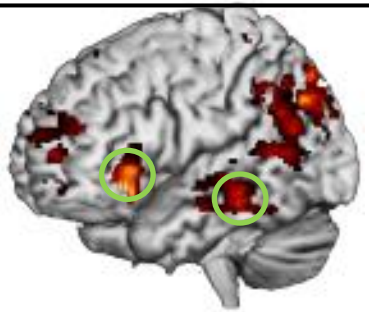
Train on individual participants' patterns of brain activity

ASD *or* TD?



Test on Left Out Participants' maps

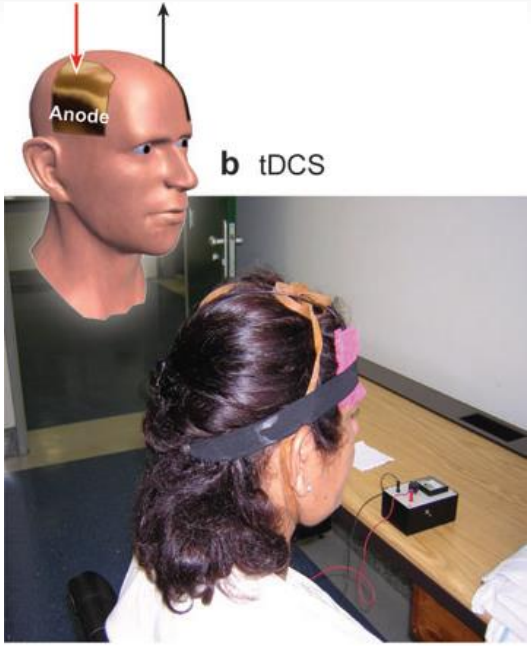
BRAIN AREAS

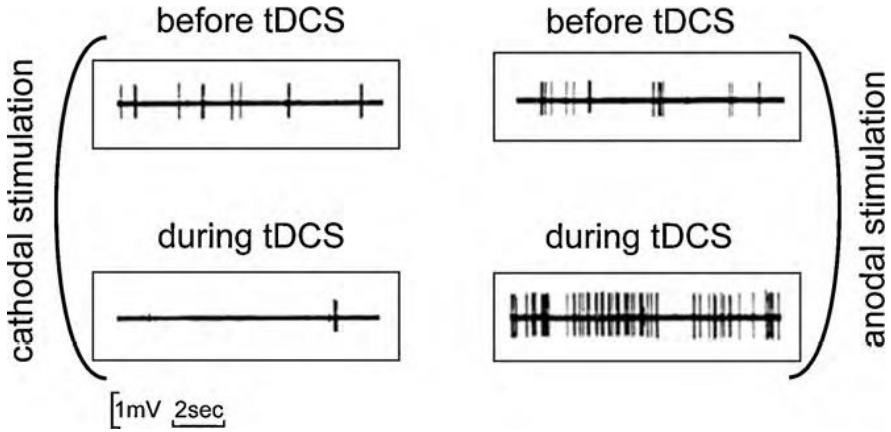


Brain areas that show differences in multivariate brain activity patterns between ASD and TD

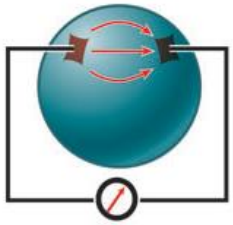
Abrams et al., 2013; Cho et al., 2011; Iuculano et al., 2014; Uddin et al., 2011. 2013

tDCS



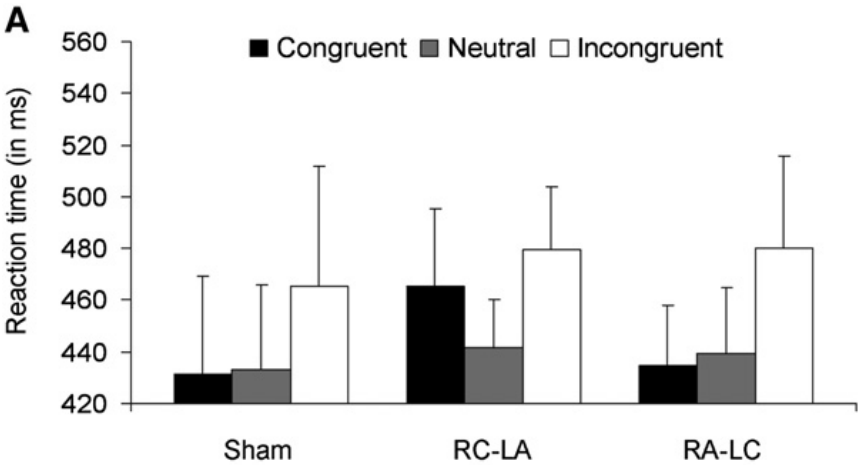


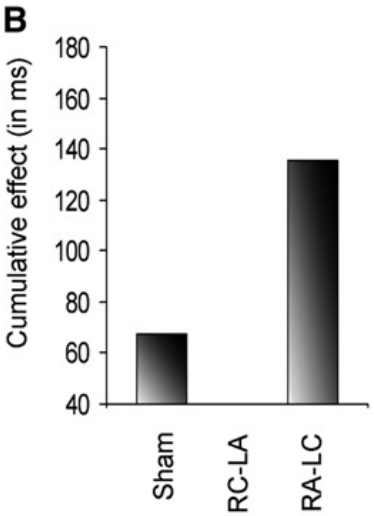
DC current applied via pair of electrodes; current induced in conductor

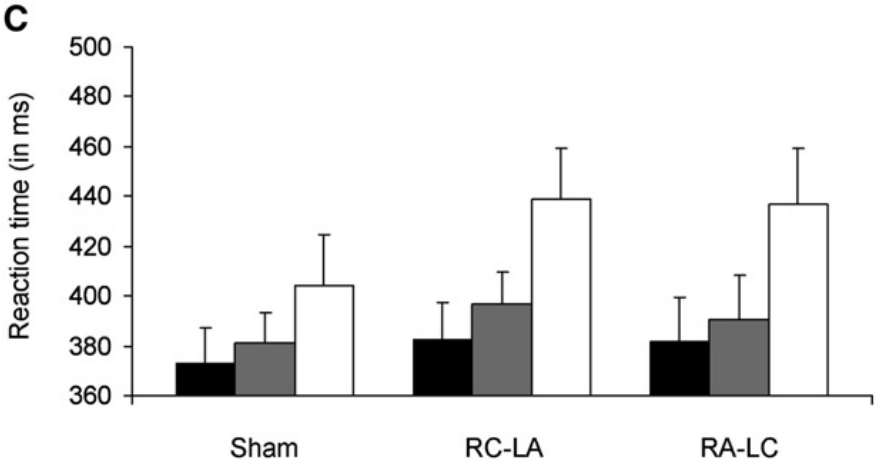


Wagner et al. (2007). Annu.Rev.Biomed.Eng.

Anodal stimulation to the PPC improves numerical skills



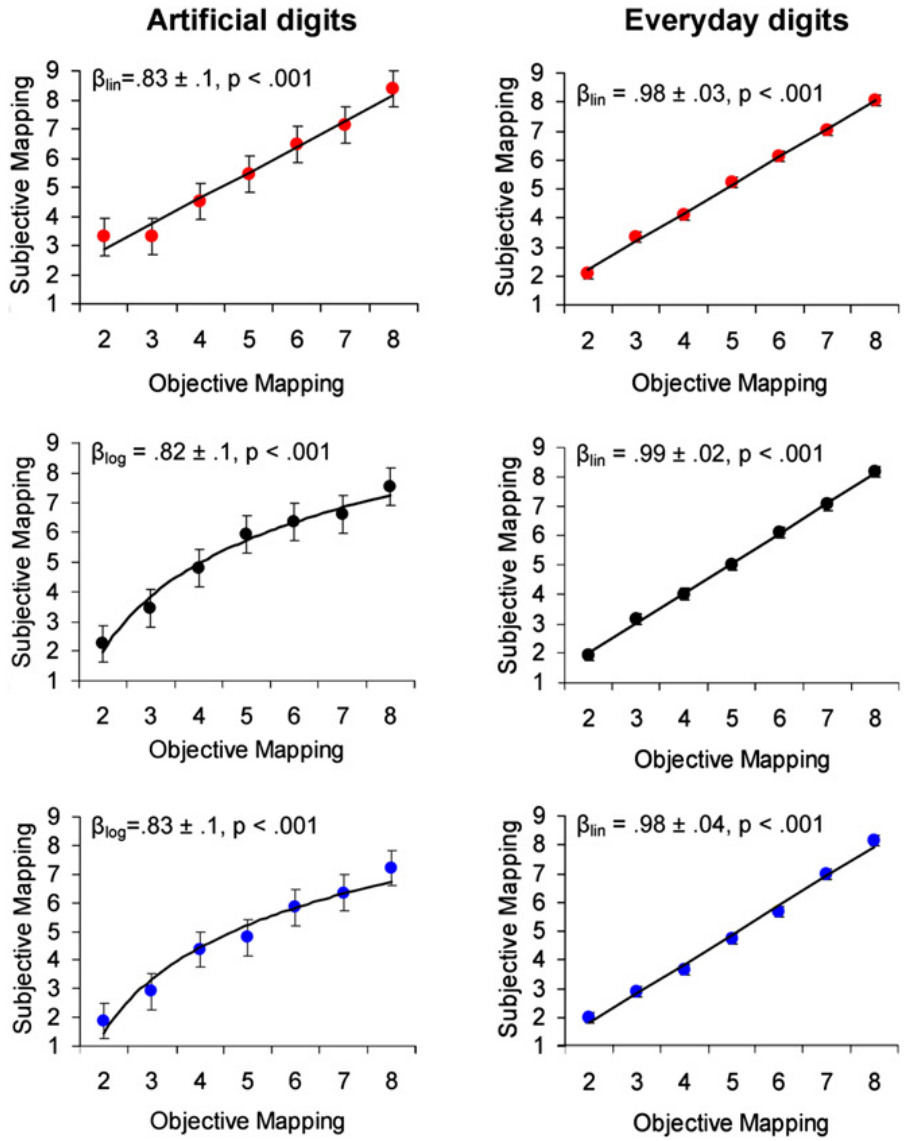




			2nd session	3rd session	4th session	5th session	6th session
Sham	Congruent	RT	593	461	456	**447**	**415**
		SEM	51	20	24	**51**	**26**
	Neutral	RT	510	466	438	**442**	**424**
		SEM	33	12	19	**36**	**30**
	Incongruent	RT	581	470	466	**495**	**436**
		SEM	44	17	18	**65**	**31**
Right Cathodal	Congruent	RT	519	473	483	428	424
		SEM	52	24	40	29	20
	Neutral	RT	487	441	465	412	401
		SEM	33	29	33	15	13
	Incongruent	RT	561	464	499	437	436
		SEM	45	25	39	22	12
Right Anodal	Congruent	RT	513	447	**430**	**433**	**441**
		SEM	41	27	**25**	**37**	**13**
	Neutral	RT	523	447	**443**	**435**	**440**
		SEM	44	20	**22**	**37**	**20**
	Incongruent	RT	524	448	**480**	**476**	**485**
		SEM	52	22	**34**	**47**	**35**

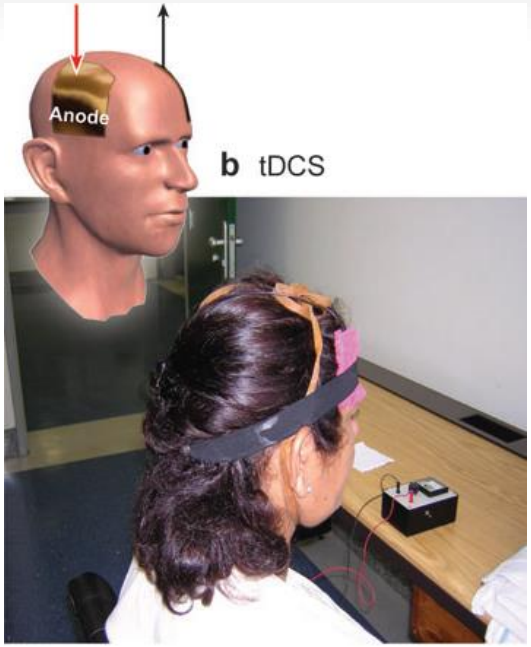
Cohen Kadosh et al., 2010

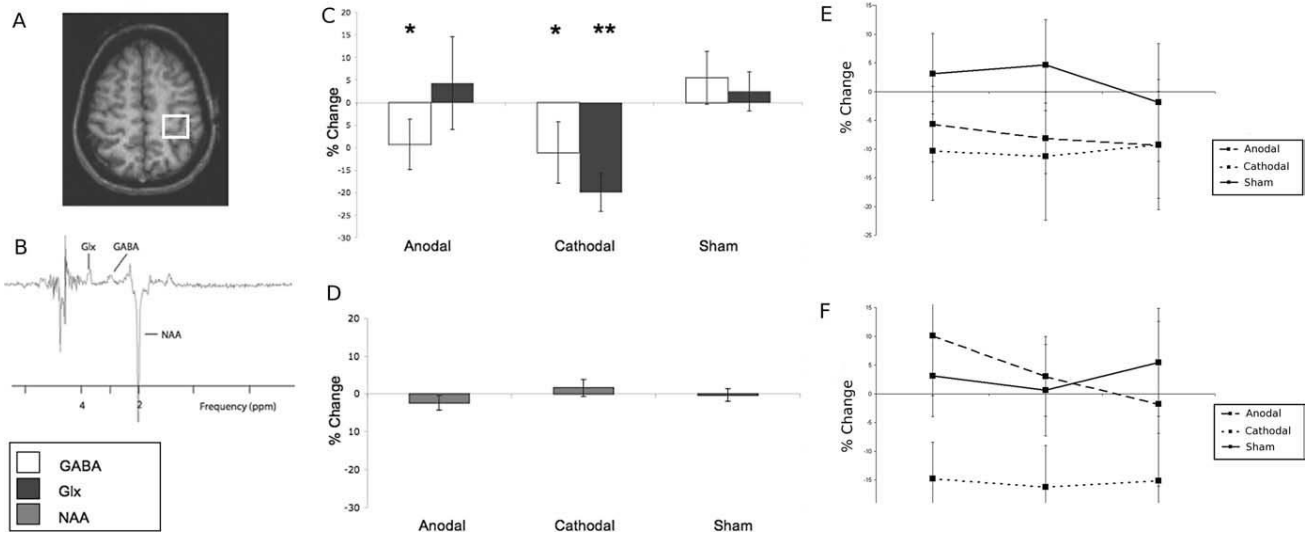
Anodal stimulation to the PPC improves numerical skills



Cohen Kadosh et al., 2010

tDCS





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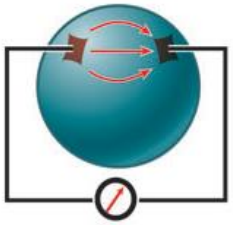

Neuro-modulation technique

Low-amplitude direct currents – applied via scalp electrodes - **modify transmembrane neuronal potential** (depolarize or hyperpolarize) ithus nfluencing **the level of excitability** by **modulating** the **firing rate** of **individual neurons**

Wagner et al. 2007

Stagg et al., 2009